IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re:	Application No. 10/091,538	*Confirmation No. 8240*
Filed:	March 7, 2002	
Applicant:	Deb CHATTERJEE et al.	**EFS MAILED: August 11, 2008** using the USPTO's EFS-Web.
Title:	IMPROVED IN VITRO SYNTHESIS SYSTEM	
Art Unit:	1652	
Examiner:	Rebecca Prouty	
Docket No.:	IVGN 300	

REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir or Madam:

On May 3, 2007, the Examiner made a final rejection to pending Claims 1, 16-17, 28, 30, 41, 51-55, 57, 60-62, 69-70, 77-78, 85-87 and 91-96. An Appellants' Appeal Brief was filed February 1, 2008 and a supplemental brief was filed March 12, 2008. An Examiner's Answer was mailed on June 10, 2008.

The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed since August 10, 2008 was a Sunday.

It is not believed that extensions of time or other fees are required in this electronic filing. However, if any further extension(s) of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R.

§ 1.136(a), and any fees required are hereby authorized to be charged to our Deposit Account No. 50-3994.

ARGUMENTS

A. Claims 1, 16-17, 28, 30, 41, 51-55, 57, 60-62, 69-70, 77-78, 85-87 and 91-96 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Pratt et al. (1984) (Pratt) in view of Yu et al. (2000) (Yu).

The Examiner cites the following arguments in support of this rejection:

1) The instant rejection is a 103 rejection and NOT a 102 rejection such that all elements of the claim need not be present in either of Pratt or Yu alone but only in the combination thereof. All elements of the recited claims are in fact present in the combined disclosures of Pratt and Yu (emphasis in original, Page 9, paragraph 1 of the Examiner's Answer).
2) Pratt clearly teach an E. coli cell used to make an ITT (an *in vitro* transcription-translation) extract and ITT systems.... in which the cell does not express Gam (i.e., E. coli MRE600). (Page 9, paragraph 1 of the Examiner's Answer)
3) Yu et al. teach the lambda (λ) Gam protein and teach its addition to an E. coli **cell** (not cell extract) (emphasis added- Page 9, paragraph 1 of the Examiner's Answer). As such, both Pratt and Yu teach that the use of a mutant strain lacking the E. coli recBCD exonuclease (which) has both desirable benefits as well as substantial shortcomings for a desired method. Yu teach that the solution to this is to replace the use of the mutant strain with a wild type strain in combination with the λ Gam protein, which is an inhibitor of the recBCD protein. A skilled artisan would have found it obvious to combine Pratt and Yu as the problem to be solved is the same for both types of systems (Page 5, last line to page 6, paragraph 1 of the Examiner's Answer).

Appellants strongly disagree.

Arguments

Central to all of the Examiner's arguments is the alleged assertion that the IVTT (*in vitro* transcription-translation) system or composition or kit, which uses a mutant E. *coli* extract with

the addition of the λ Gam protein, as is instantly claimed, would have been obvious to one of ordinary skill in the art.

Appellants strongly disagree. To establish a *prima facie* case of obviousness, the Patent Office must articulate "reasoning with some rational underpinning to support the legal conclusion of obviousness" (MPEP 2142, citations omitted). Further, the Examiner must show that Pratt and Yu convey to the skilled artisan a reasonable expectation of success in preparing the claimed subject matter (MPEP 2143.02). To find a reasonable expectation of success, Pratt and Yu must be considered in their entirety, including protions that would lead away from the claimed invention (MPEP 2141.02(VI)). Viewed as a whole, Pratt and Yu would NOT lead the skilled artisan to the present claims. In fact, the only plausible way to arrive at the claimed subject matter from these references is by using impermissible hindsight.

The present independent claims are directed to an in vitro protein or nucleic acid synthesis system, kit or composition. The system includes at least one extract from an E. coli cell that does not express Gam and that has reduced activity of a nuclease as a result of mutation. The extract is modified by the addition of Gam protein. The specification explains that the Gam protein utilized in the *in vitro* synthesis system may be a soluble Gam protein. The specification further explains that the at least one nuclease in the in vitro system may be a DNase, which may include exonuclease I, exonuclease II, exonuclease III, exonuclease IVA, exonuclease IVB, RecBCD (exonuclease V), exonuclease VII, exonuclease VIII, RecJ, dRpase, endonuclease I, endonuclease III, endonuclease IV, endonuclease V, endonuclease VII, endonuclease VIII, endonuclease A, fpg, uvrABC, mutH, vsr endonuclease, ruvC, ecoK, ecoB, mcrBC, mcrA, mrr, topoisomerase I, topoisomerase II, topoisomerase III, or topoisomerase IV.

Pratt's teachings coincide with the instant specification's teachings in that it discloses the use of a mutant E. coli extract for IVTT systems; for e.g., it discloses an E. coli MRE600 S30 extract (which lacks RNase) in an IVTT system. The Examiner acknowledges that Pratt does not teach combining its IVTT system with the use of a λ Gam protein (see page 9, lines 13-15 of the Examiner's answer). Appellants respectfully submit that the Examiner has misrepresented some aspects of Pratt's teachings because Pratt does not teach the "use of a mutant strain lacking the E. coli recBCD exonuclease" for IVTT, as the Examiner contends (see Examiner's comment on page 5, last line to page 6, paragraph 1 of the Examiner's Answer). In fact, mutant strains other than the E. coli MRE600 S30 extract (which lacks RNAse, not rec BCD exonuclease

as the Examiner contends) were NOT disclosed, and no reference was made to using mutant strains lacking DNAses (exonucleases), let alone mutants lacking E. coli recBCD exonuclease, for IVTT. Therefore, one skilled in the art could not have thought of combining Pratt with the λ Gam protein (which is an inhibitor of the E. coli recBCD exonuclease), because the E. coli recBCD exonuclease was not identified as a problem in Pratt's IVTT system.

Yu teaches mutant exonucelase deficient strains. For instance, Yu discloses that: "mutant recBCD strains lacking the exonuclease do not rapidly degrade linear DNA; however such strains are extremely poor growing, are defective for recombination, and do not support efficient replication of the any plasmids used in recombinant DNA work" (see Yu, page 5978, column 1, second paragraph, line 3). Yu teaches and advocates the use of the λ prophage system as an efficient recombination system for rescuing recombination (not IVTT) in nuclease-deficient systems. Yu examined several parameters that are required for maximal and efficient phage-mediated recombination. To do this, Yu made an E. coli strain that harbors the λ prophage containing the recombination genes gam, bet, exo under temperature-sensitive control (see Yu, page 5978, column 1, second paragraph, line 3). Yu did not teach the addition of the Gam protein, but rather teaches the phage-induced expression of the gam gene, together with genes bet and exo. Maximal induction levels were achieved with induction times from 7.5-17.5 min at 42°C (see Yu, page 5982, column 2, paragraph 1). Therefore, Yu's system requires an **intact E. coli cell** for the λ prophage-induced expression of the Gam protein. That is, Yu's temperature sensitive induction of the gam, bet, and exo expression cannot occur in the E. coli BCD$^-$ cell extract and therefore, even by inference, Yu does not teach or suggest the use of gam or Gam protein in a cell extract system. Another important point to note is that, Yu teaches the expression of three recombination genes, namely, gam, bet, and exo genes (not gam alone) to rescue recombination. In addition, on Table 1, Yu enlists various bacterial strains that are compatible for such λ prophage work, which did NOT include Pratt's RNase$^-$ E. coli MRE600 mutant strain.

Taken together, the skilled artisan would not be motivated to combine Yu's λ gam gene expression in Pratt's RNase$^-$ E. coli MRE600 S30 cell extract, because: (1) any teaching for combining the Gam protein with a **cell extract** is absent in both references, (2) the two systems are incompatible; that is, Yu's system requires an intact cell system for the temperature sensitive expression of the gam gene, whereas Pratt's system uses a cell extract, that does not require

Gam protein, (3) Yu's teachings are directed to improving recombination in nuclease-deficient systems, whereas Pratt teaches cell-free IVTT systems; [Appellants note that the Examiner erroneously concludes that "the problem to be solved is the same for both types of systems"]. In fact, in light of these teachings, a skilled artisan would have been dissuaded from combining Yu's and Pratt's systems to perform IVTT.

Even if, arguendo, one skilled in the art combined the teachings of the two references, as such, they would have to conduct further experiments and further, may not have had reasonable expectations to succeed because: (1) based on Yu's Table 1, which does NOT include Pratt's RNase- E. coli MRE600, further experimentation would have been necessary for the E. coli MRE600 cell line; (2) all three recombination genes, namely, gam, bet, and exo gene expressions would be necessary because of Yu's clear teachings: "Table 3 shows that only exo, bet and gam deletions affected gal K<> tet targeted recombination. **Deletion of any one of these three genes eliminated the recombination**… (emphasis added- see Yu, page 5982, column 1, paragraph 3, line 7 onwards). So, even if, arguably, the proteins GAM, BET, and EXO were expressed and added to the E. coli MRE600 cell-extract system for IVTT, this does not result in the Appellant's invention. So, the combined teachings of Yu and Pratt do not result in the Appellants' disclosure and claimed invention.

Therefore, arriving at the present claims by selecting certain teachings of the cited references and ignoring other teachings in the same reference can only be done using impermissible hindsight. As such, the Examiner has failed to establish a *prima facie* case of obviousness, because even the improperly combined teachings of the references fail to teach the claim elements of the present invention.

Moreover, the present claims are not "obvious to try" because, to achieve the goal of the present invention would require the artisan to act contrarily to other teachings within the same cited reference. For instance, Yu's system requires an intact cell system for the temperature sensitive expression of the gam, exo, bet genes, whereas Pratt's system teaches a cell extract system that does not require these proteins. Why would a skilled artisan want to try a cell extract system when Yu's system clearly calls for an intact prophage system?

Clearly, all of the conditions for rejection of the claim under 35 U.S.C. § 103(a) are not met, and as such, the Examiner has failed to establish a *prima facie* case of obviousness. Appellants respectfully request that the rejection of pending claims be withdrawn.

B. Claims 86-87, 89, 90, 92, 93, 95-96 stands rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Pratt (1984) in view Yu et al., and further in view of Swartz et al. (WO 00/55353).

Arguments

The Examiner indicates that Appellants have not presented any arguments specifically traversing this rejection (see page 14, part (B) of the Examiner's answer).

Appellants strongly disagree. Appellants distinctly argued this rejection in their Appeal Brief filed February 1, 2008, on page 11, under Section VII (B). Moreover, the rejected claims depend directly or indirectly from the independent claims. For instance, claims 86 and 87 depend indirectly from independent claim 1, claims 92 and 93 depend indirectly from independent claim 41, and claims 95 and 96 depend indirectly from independent claim 51. The independent claims have been argued above under Section VII (A), and those arguments are incorporated by reference herein. In addition, Swartz does not make up for the deficiencies of Pratt and Yu et al., in that Swartz also does not disclose or suggest Gam protein or the addition of Gam protein to an E. coli lysate, and therefore, does not compensate for deficiency in the combined teachings of Pratt and Yu et al.

Since all the elements of the invention are not disclosed in the combined teachings of the primary references, Pratt and Yu et al., and further, neither in the secondary reference, Swartz et al., this U.S.C. §103(a) rejections falls. Thus, the rejected claims are not obvious and accordingly, this rejection should be withdrawn.

C. Claims stands rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over 61, 62, 69, 70, 77 and 78 are not obvious over Pratt in view of Yu et al. and further in view of Swartz and further in view of Kudlicki et al.

Arguments

The Examiner indicates that Appellants have not presented any arguments specifically traversing this rejection (see page 14, part (C) of the Examiner's answer).

Appellants strongly disagree. Appellants had distinctly argued this rejection in their Appeal Brief filed February 1, 2008, on pages 11-12, under Section VII (C). Moreover, the rejected claims depend directly or indirectly from the independent claims. For instance, Claims 61 and 62 depend indirectly from claim 1, claims 69 and 70 depend indirectly from claim 41, and claims 77 and 78 depend indirectly from claim 51.

The independent claims have been argued above under Section VII (A), and those arguments are incorporated by reference herein. In addition, Kudlicki does not make up for the deficiencies of Pratt, Yu et al., or Swartz, in that Kudlicki does not disclose or suggest the Gam protein or the addition of the Gam protein to an E. coli lysate, and therefore, does not compensate for deficiency in the combined teachings of Pratt and Yu et al. or Swartz.

Since all the elements of the invention are not disclosed in the combined teachings of the primary references, Pratt and Yu et al., and further, neither in the secondary references, Swartz et al., or Kudlicki, this U.S.C. §103(a) rejections falls. Thus, the rejected claims are not obvious and accordingly, this rejection should be withdrawn.

Conclusion

In view of the foregoing, Appellants respectfully request reversal of the Examiner's final rejections.

Respectfully submitted,

/Daphne Reddy/

Daphne Reddy, Reg. No. 53,507
Invitrogen Corporation
Customer No. 52059
Phone: (760) 268-8397

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